Homeostatic plasticity of the mitochondrial proteome and lipidome upon stress

Mitochondria are essential organelles within our cells that allow us to live. They transform the oxygen from our lungs and glucose from our food into the cell's energy currency ATP and are thus commonly known as the 'powerhouse of the cell'. However, mitochondria are also involved in many more important roles in the body that researchers continue to learn about, e. g. in communication and metabolite production. Unfortunately, we often learn about the important roles of any parts of our bodies when they malfunction, as in diseases. In the case of mitochondria and their vital functions, various dysfunctions can cause many dangerous diseases. In general, health can be described as a system that is kept in balance, or simply by the Greek term homeostasis ('staying the same'). Diverse sources of stress can cause a system to become out of balance, resulting in disease. Stress on mitochondria can occur during all stages of life and be brought about by, for example, detrimental inherited genetic disorders in newborns as well as during the aging process resulting in neurodegenerative disorders.

In order to combat such mitochondrial pathologies, there is a great need for understanding what is happening on the molecular level during stress. Many scientists have explored this question by comparing healthy cells to stressed cells and gained important insights into the molecules that are increased and decreased with stress. One class of molecules that researchers are especially interested in are proteins. These crucial biomolecules often function as enzymes carrying out the reactions within our cells, such as the proteins constituting the electron transport chain that carries out the most important function of mitochondria. In addition to proteins, we want to study lipids, another abundant biomolecule of mitochondria. Lipids, better known as fats, are molecules that constitute the membranes of whole cells and mitochondria, but certain lipids also serve signaling and hormone functions. Mitochondria share many of the same lipids as cells, but also contain special ones, such as their signature lipid cardiolipin. We believe that by measuring both proteins and lipids in our experiments, we will be able to better understand how these two molecules interact upon stress.

We will use a technology called mass spectrometry that allows us to measure quantities and identities of many of these biomolecules at the same time. A mass spectrometer functions like a molecular scale by determining the exact mass of each biomolecule in a sample. Since all molecules are made up of the same building blocks, their exact mass can reveal their unique composition, thus allowing for identification of the protein or lipid. Furthermore, the intensity count of each molecule's signal is proportional to its abundance in a sample, thus allowing for comparison between different samples.

We can learn a lot from nature therefore an important step in research is to study of the cell's own stress combat mechanisms. We will investigate the cells' dynamic adaptation to mitochondrial stress with a tailored system that uses CRISPR-Cas9 technology to insert a switch that allows us to flip the stress on and off. The stress in our case is the so-called knocking out of key genes, which then cannot produce their respective protein, mimicking damage due to degenerative processes or genetic disorders. We believe that this reversible system allows for a more accurate modeling of the cellular stress response over time back to a homeostatic state. With this research project, we hope to identify biomolecules that are important for maintaining mitochondrial homeostasis. These could be individual proteins or lipids, but also bigger complexes of multiple proteins and even protein complexes that interact with lipids.

Once we identify these molecules as likely involved in mitochondrial stress, we will then closely examine them with a special mass spectrometry technique that keeps these macromolecular complexes in their native-like state. This will allow us to better understand what their roles are and how they interact. Identification of individual stress response pathways and, more generally, a better molecular understanding of how cells deal with stress are not only important out of pure academic interest but are also the basic requisite for developing treatments and preventative measures against diseases.